LECTURE

What Have We Accomplished (and What Lies Ahead)

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INTRODUCTION

The idea of holding consensus meetings on portal hypertension was born in 1986, when Andrew Burroughs organised the first such meeting in Groningen, the Netherlands [1]. After Groningen, other meetings followed, in Baveno, Italy in 1990 (Baveno I) [2] and in 1995 (Baveno II) [3,4], in Milan, Italy in 1992 [5], in Reston, United States [6] and in Stresa, Italy in 2000 (Baveno III) [7,8]. This is the seventh meeting of this kind.

In this review, I will summarise the work previously done in the Baveno workshops I to III and outline the new diagnostic and therapeutic modalities that are emerging and will have to be evaluated in the near future.

What we have done

1 Topics covered at the Baveno I, II and III meetings.
2 Publications derived from the Baveno I, II and III workshops.
3 Quantitative impact of the Baveno I, II and III consensus on the medical literature.
4 Attendance at the Baveno workshops.

What lies ahead

1 New diagnostic tools.
2 New drugs.
3 New therapeutic strategies.

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WHAT WE HAVE DONE

Topics addressed at the Baveno I, II and III workshops

- Definitions of key events.
- Diagnostic evaluation of patients with portal hypertension.
- Prognostic factors for first bleeding, rebleeding and survival.
- Therapeutic strategies in patients with portal hypertension.
- Methodological requirements of future trials.

Publications derived from the Baveno I, II and III workshops

- The Baveno I workshop was reported in the *Journal of Hepatology* in 1992 [2].
- A report of the Baveno II workshop was published in the *Journal of Hepatology* in 1996 [3].
- The proceedings book of the Baveno II workshop was published by Blackwell Science in 1996 [4].
- The Baveno III workshop was reported in the *Journal of Hepatology* in 2000 [7].
- The proceedings book of the Baveno III workshop was published by Blackwell Science in 2001 [8].

Impact of the Baveno consensus on the medical literature

Figure 1 shows the number of citations of the Baveno I–III reports in the medical literature between January 1993 and January 2005. Overall, the reports had more than 200 citations.

Attendance at the Baveno workshops

Two hundred and five participants took part in the Baveno I workshop; 81% of them were from Italy, 19% from other countries. Eighteen countries were represented.

The Baveno II workshop was attended by 252 participants, of which 74% were from Italy and 26% from other countries. Eighteen countries were represented.

The attendance of the Baveno III workshop was 385, of which 49% were from Italy and 51% from other countries. Twenty-nine countries were represented.

Four hundred and eighty five participants took part in the Baveno IV workshop; 38% were from Italy, 62% from 39 other countries. Forty countries were represented: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Costa Rica, Croatia, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Jordan, Korea, Malaysia, Mexico, Pakistan, Portugal, Romania, Saudi Arabia, Serbia-Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, The Netherlands, United Kingdom and United States.

These data are shown graphically in Figs 2 and 3.

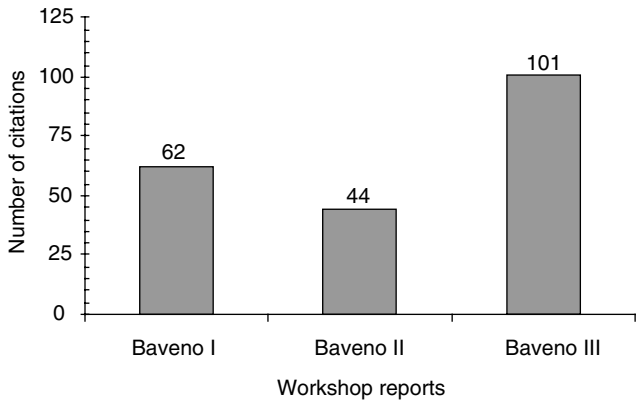

Fig. 1 Citations of the Baveno I–III reports.

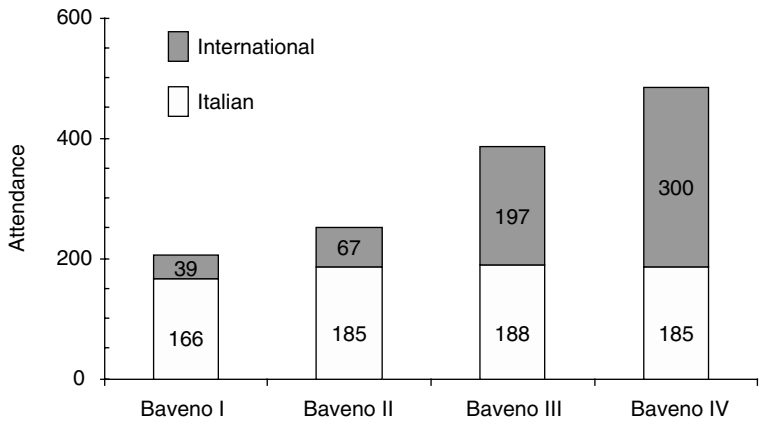

Fig. 2 Attendance at the Baveno I–IV workshops.

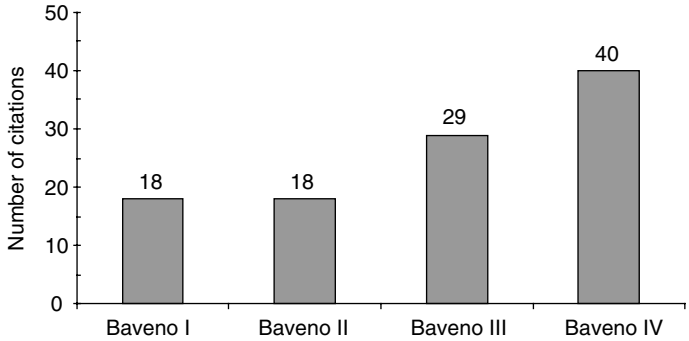

Fig. 3 Countries represented at the Baveno I–IV workshops.

WHAT LIES AHEAD

New diagnostic tools

Oesophageal endoscopic capsule (PillCam Eso)

Traditionally, upper GI endoscopy (EGD) has been the mainstay for the diagnosis of portal hypertension. Current guidelines [7] recommend that all cirrhotic patients be screened for oesophageal varices by endoscopy at the time of the diagnosis of cirrhosis: those with no varices at screening endoscopy should undergo endoscopic surveillance every 2–3 years; those with small varices at screening endoscopy should undergo endoscopic surveillance every 1–2 years.

These recommendations represent a potentially large endoscopic burden. Their application is hampered by suboptimal patient acceptance of conventional EGD. The availability of a less invasive screening test could improve patient acceptance and thus adherence to recommendations.

The recently developed oesophageal capsule endoscope (PillCam Eso®) is a new, minimally invasive tool for the study of oesophageal lesions. Plate 1 (*facing p*. 204) shows the appearance of oesophageal varices on PillCam Eso® endoscopy. In a pilot study [9], the PillCam Eso® has been compared with conventional EGD for the diagnosis and surveillance of oesophageal varices in cirrhotic patients. The study has shown a 96.9% agreement between PillCam Eso® and EGD for the diagnosis of the presence of oesophageal varices. The sensitivity, specificity, positive and negative predictive values of PillCam Eso® were 100%, 89%, 96% and 100% respectively (Fig. 4). If these data are confirmed, the PillCam Eso® could become a first-line, minimally invasive tool to screen cirrhotic patients for the presence of varices.

		Traditional Endoscopy +	Traditional Endoscopy −	
Capsule endoscopy	+	23	1	24
	−	0	8	8
		23	9	32

Overall agreement 96.9%

Positive likelihood ratio: 9.1

Negative likelihoodratio: 0.0

	Capsule endoscopy
Sensitivity	100%
Specificity	89%
PPV	96%
NPV	100%

Fig. 4 Comparison of EGD and PillCam Eso® for the diagnosis of oesophageal varices.

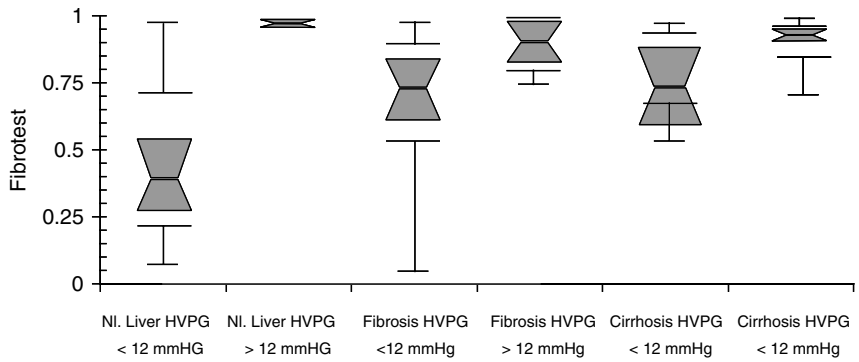

Fig. 5 Relationship between Fibrotest values and degree of portal hypertension in patients with normal liver, liver fibrosis and cirrhosis.

Fibrotest and Fibroscan

Attempts at identifying the patients with oesophageal varices by non-invasive means, in order to restrict the performance of endoscopy to the patients with a high probability of having varices have been disappointing so far [10]. It has been suggested that patients with varices could be identified non-invasively by a combination of biochemical tests [α-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyltranspeptidase and total bilirubin (Fibrotest)] and/or by transient elastography (Fibroscan). A French study [11] presented in 2004 at the AASLD meeting has shown that there is a good correlation between the values of Fibrotest and the presence of severe portal hypertension (Fig. 5). Another recent study [12] has shown a good correlation between liver stiffness measured by transient elastography and

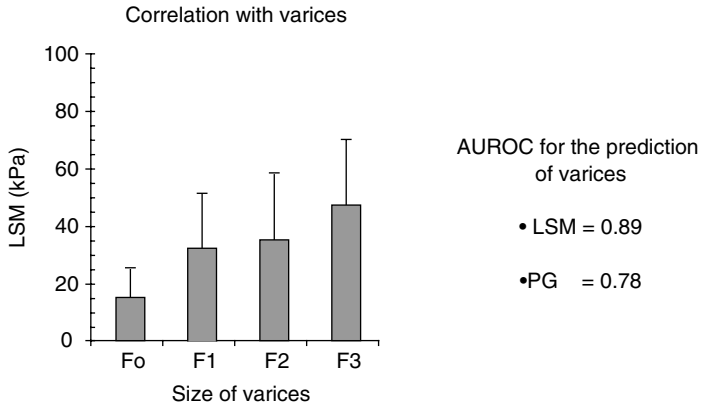

Fig. 6 Relationship between liver stiffness measured by transient elastography and presence and size of oesophageal varices (left panel). Comparison of the area under the ROC curve (AUROC) for transient elastography (LSM) and portal pressure gradient (PG) (right panel).

the presence and size of oesophageal varices (Fig. 6). Further studies with the above techniques should be carried out to define whether Fibroscan and/or Fibrotest can be used to identify non-invasively the patients with oesophageal varices.

New drugs

Interferon in the prevention of the progression of fibrosis

Attempts at preventing the development of oesophageal varices with β-blockers have given disappointing results [13,14]. The recent demonstration that interferon treatment may delay the development of varices in patients with chronic hepatitis C and hepatitis C virus (HCV)-related cirrhosis [15] (Fig. 7) suggests that interferon treatment might have a role in preventing the development of portal hypertension. this hypothesis deserves to be tested in appropriately designed studies.

Recombinant-activated factor VII (rFVIIa) in the treatment of acute variceal bleeding

It has recently been shown that the administration of recombinant-activated factor VII (rFVIIa) normalises prothrombin time in bleeding cirrhotic patients. The potential role of rFVIIa has been evaluated in a multicentre European trial [16], including 245 bleeding cirrhotic patients who were

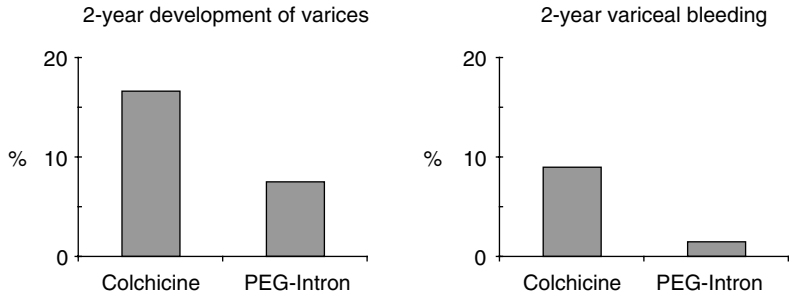

Fig. 7 Comparison between PEG-Interferon and colchicine in the prevention of the development of oesophageal varices and of variceal bleeding in patients with chronic hepatitis C and with HCV-related cirrhosis.

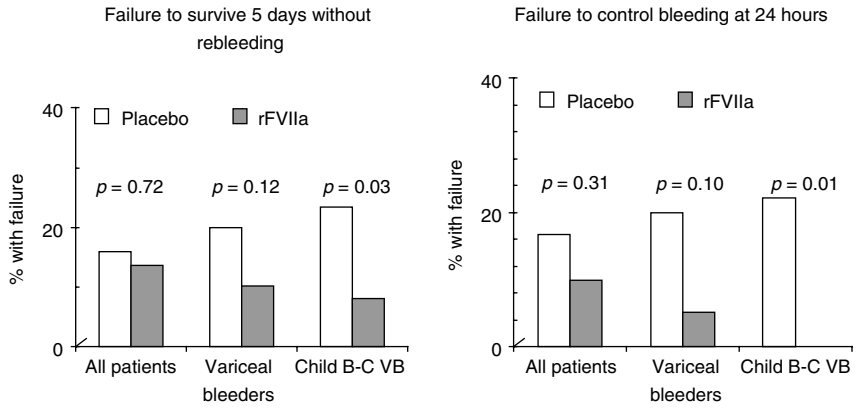

Fig. 8 Randomised controlled trial of recombinant-activated factor VII (rFVIIa) as an adjunct to endoscopic and vasoactive treatment for acute variceal bleeding.

randomised to receive eight doses of rFVIIa, 100 μg/kg or placebo in addition to combined endoscopic + pharmacological treatment. The primary end point was a composite including failure to control bleeding at 24 h, failure to prevent rebleeding between 24 h and 5 days and death within 5 days. No significant effect was found when analysing the whole patients population; however, an exploratory analysis showed that, in Child-Pugh B and C variceal bleeders, rFVIIa significantly reduced the occurrence of the primary end point (from 23% in patients receiving placebo to 8% in patients receiving rFVIIa, $p = 0.03$), and improved bleeding control at 24 h (from 88% to 100%, $p = 0.03$) (Fig. 8). These data are encouraging, but require confirmation by studies specifically targeted on the appropriate patients.

Conclusions

All these exciting new developments will have to be carefully evaluated to see whether they can be incorporated in the diagnostic/therapeutic armamentarium for portal hypertension.

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